UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/810,358	03/26/2004	Ker-Sang Chen	9188R&	1244

27752 7590 08/27/2010

THE PROCTER & GAMBLE COMPANY
Global Legal Department - IP
Sycamore Building - 4th Floor
299 East Sixth Street
CINCINNATI, OH 45202

EXAMINER	
SHAFER, SHULAMITH H	
ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
08/27/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/810,358	CHEN ET AL.	
	Examiner	Art Unit	
	SHULAMITH H. SHAFER	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-8,11-21 and 24-49* is/are pending in the application.

4a) Of the above claim(s) *13-15 and 24-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-8,11,12,16-21,46-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

Applicants' submission and amendment of 21 June 2010 is acknowledged. Claims 46-49 are newly submitted and entered into the record.

Claims 1, 3, 5-8, 11-21 and 24-49 are pending in the instant application. Claims 13-15 and 24-45 stand withdrawn as being drawn to a non-elected invention.

Claims 1, 3, 5-8, 11, 12, 16-21 and 46-49 are under consideration.

Maintained/New Grounds of Objection/Rejection

Objections

Claims:

Claim 48 is objected to because of the following informalities: There is a typographical error in the claim in line 1 (the_level). Appropriate correction is required.

Rejections

35 U.S.C. § 103:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The rejection of Claims 1, 3, 5, 16, 17, 19 and 20 under 35 U.S.C. 103(a) as being unpatentable over Togawa et al. (2002 Am J. Physiol, Gastrointestinal Liver Physiol 283:G187-G195) in view of Hart et al. (2003. J. Clin Gastroent 36:111-9) is maintained and applied to newly submitted claim 46 for reasons of record and for reasons set forth below.

The cited references establish the following fact pattern:

Togawa et al teach that there is a disturbed balance between proinflammatory and anti-inflammatory cytokines in inflammatory bowel disease (page G187, 2nd column, 1st paragraph). The reference teaches administration of lactoferrin to rats with TNBS-induced inflammatory bowel disease, a well-established model of human inflammatory bowel disease, which responds favorably to therapies for IBD (page G192, 2nd column, 2nd paragraph). Concentrations of cytokines were measured in inflamed colonic tissue (biopsy sample) in animals with TNBS-induced IBD without treatment and in animals with TNBS-induced IBD treated with lactoferrin seven days after TNBS administration (page G188, 2nd column, last paragraph bridging G189, 1st column, 1st paragraph, page G191, 1st column, last paragraph bridging 2nd column, first paragraph and Figure 5). Concentrations of pro-inflammatory cytokines TNF-α, IL-1β and IL-6 and anti-inflammatory cytokines IL-4 and IL-10 (abstract, page G-189, 1st column, 1st paragraph and Figure 5) were determined by ELISA assay (page G189, 1st column, 1st paragraph). Togawa et al. teach that administration of lactoferrin in TNBS-treated rats attenuated all of the inflammatory responses, concluding that the lactoferrin obviously suppressed TNBS-induced colitis (page G192, 2nd column, 2nd paragraph). This correlated with suppression of activation of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 and activation of anti-inflammatory cytokines IL-4 and IL-10 (page G192, 2nd column, 2nd paragraph, bridging page G193, 1st column, 2nd paragraph). The reference thus teaches a change in levels of pro-inflammatory and anti-inflammatory cytokines in

response to lactoferrin treatment which correlates with attenuation of inflammatory symptoms of IBD. The change in cytokine profile thus correlates with efficacy of treatment, in this instance, administration of lactoferrin.

Hart et al. teach animal models and controlled clinical studies have demonstrated the efficacy of probiotics in treatment of Crohn's disease (abstract), an inflammatory bowel disease. The reference teaches that patients with Crohn's disease treated with pro-biotics showed significant reduction in disease activity (page 115, 2nd column). The reference teaches that strains of probiotics alter the activity and cytokine production of gut-associated lymphoid tissue and epithelial cells; probiotic bacteria have been shown to increase mucosal production of IL-10 (an anti-inflammatory cytokine) and reduce the secretion of TNF-α, IFN-γ (page 116, 2nd column, 4th paragraph) and IL-12 (page 117, 1st column, 1st paragraph). The reference thus teaches a correlation between amelioration of IBD symptoms and change in cytokine profile.

Both cited references thus teach that amelioration of symptoms of IBD are correlated with an increase in expression of anti-inflammatory cytokines (IL-4, and IL-10) and a decrease in expression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IFN-γ and IL-12).

The references, singularly or in combination, do not teach a method comprising measuring the level of at least one anti-inflammatory and one pro-inflammatory cytokine in a biological sample and determining the ratio of the level of the at least one anti-inflammatory and the at least one pro-inflammatory cytokine before administration of treatment and determining the ratio of the level of the at least one anti-inflammatory and the at least one pro-inflammatory cytokine after treatment.

However, in view of the facts set forth above, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the prior art elements according to known methods to yield predictable results.

Togawa et al. teach measurement of pro-inflammatory and anti-inflammatory cytokines in colonic samples from untreated IBD animals and IBD animals treated with lactoferrin. The skilled artisan, following the teaching of Togawa et al, would be motivated to measure cytokine levels before treatment in a clinical setting, instead of

measuring levels in control animals, as the artisan would be aware of that such study design is standard protocol in clinical research and clinical practice.

Togawa et al does not teach a method of determining the efficacy of a probiotic as a treatment of inflammatory diseases of the bowel in mammals. However, aware of the teachings of the Hart et al. reference, which teaches the efficacy of administration of pro-biotics as a treatment for inflammatory bowel disease in mammals, including humans, and that such treatment has been shown to increase mucosal production of IL-10 (an anti-inflammatory cytokine) and reduce the secretion of TNF-α, IFN-γ (page 116, 2nd column, 4th paragraph) and IL-12 (page 117, 1st column, 1st paragraph), all pro-inflammatory cytokines, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute a method of determining the efficacy of a probiotic treatment of inflammatory diseases of the bowel in mammals, as taught by Hart et al for a method of determining the efficacy of lactoferrin treatment of inflammatory diseases of the bowel in mammals. One would be motivated to make such a substitution and anticipate success because both lactoferrin and probiotics are taught in the art as effective treatments for inflammatory diseases of the bowel, and having anti-inflammatory effects and the correlation of attenuation of inflammatory symptoms of IBD with increased levels of anti-inflammatory cytokines and decreased levels of pro-inflammatory cytokines is taught by Togawa et al., thus suggesting that monitoring of changing levels of cytokines would be useful in monitoring efficacy of treatment of IBD.

Additionally, neither reference, singly or in combination, directly teaches measuring the level of at least one anti-inflammatory cytokine and at least one pro-inflammatory cytokine before treatment and determining the ratio of the level of the at least one anti-inflammatory cytokine to the level of the at least one pro-inflammatory cytokine before treatment and measuring the level of at least one anti-inflammatory cytokine and at least one pro-inflammatory cytokine after treatment and determining the ratio of the level of the at least one anti-inflammatory cytokine to the level of the at least one pro-inflammatory cytokine after treatment.

However, having determined the results of measurements of cytokine levels (as shown, for example, in Togawa et al, Figure 5), one would be motivated to compute ratios as a way of efficiently determining shifts in patterns of cytokine levels. One would reasonably expect success because method of measuring cytokine levels in biological samples is well known in the art, and both references teach a correlation between attenuation of symptoms of IBD and shifts in cytokine patterns to increased levels of anti-inflammatory cytokines and decreased levels of pro-inflammatory cytokines.

With respect to newly submitted claim 46, which is directed to determining the efficacy of a probiotic treatment of inflammatory diseases of the bowel in ***humans***: One is always motivated to translate findings in animal models to clinical situations. Hart et al. teaches the efficacy of pro-biotic treatment of humans with IBD. Togawa et al teach lactoferrin may induce remission in patients with inflammatory bowel disease (G193, 2nd column, last paragraph), thus suggestion the clinical applicability of the methods taught by the reference. Thus, the teachings of the prior art, and standard clinical practice render the methods of the instant invention, as applied to humans, prima facie obvious.

Applicants traverse the rejection (Remarks of 21 June 2010, page 12, 4th paragraph). The reasons for the traversal are:

(1) The Examiner has resorted to hindsight reconstruction to supply deficiencies in required factual basis (Remarks of 21 June 2010, page 13, 2nd paragraph).

(2) Neither Togawa et al. nor Hart et aL teach or suggest determining the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment (Remarks of 21 June 2010, page 14, 2nd paragraph). Applicants submit that determining the level of at least one pro-inflammatory cytokine before and after treatment with a probiotic yields unexpected results with regard to determining the efficacy of a probiotic as a treatment of inflammatory diseases of the bowel in mammals in vivo (page 14, last paragraph). The specification of the present invention provides that, "[i]t has surprisingly been found that by increasing the ratios described herein the symptoms of inflammatory diseases of the bowel can be alleviated." (See Page 6, paragraph 0076). The specification of the

present invention also provides that, "[w]ithout wishing to be bound by theory, it is believed that the specific ratios described herein are pivotal to the progression or remission of inflammatory diseases of the bowel." (See Page 6, paragraph 0076) (page 15, 2nd paragraph).

(3) Neither Togawa et al. nor Hart et al., either singularly or in combination, teach or suggest a method of determining the efficacy of a probiotic treatment as recited in independent claim 1. Applicants submit that it would not have been obvious to one of ordinary skill in the art at the time the invention was made to substitute a method of determining the efficacy of a probiotic treatment of inflammatory diseases of the bowel in mammals as claimed for a method of determining the efficacy of lactoferrin treatment of inflammatory diseases of the bowel in mammals. The specification of the present invention provides that the very nature of inflammatory diseases of the bowel means that screening and measuring the efficacy of potential treatments in human subjects is very difficult. (See Page 1, paragraph 0008). Applicants submit that determining the efficacy of a probiotic as a treatment of inflammatory diseases of the bowel in mammals in vivo is an unpredictable art. Thus, it would not have been obvious to one of ordinary skill in the art to randomly substitute a method of determining the efficacy of a probiotic treatment of inflammatory diseases of the bowel for a method of determining the efficacy of lactoferrin treatment of inflammatory diseases of the bowel from the teachings of Togawa et al. in view of Hart et al. (page 16, 2nd-4th paragraphs).

(4) Togawa et al. and Hart et al. are completely void of any teaching or suggestion of determining the efficacy of probiotics in the treatment of inflammatory diseases of the bowel by determining the levels of various anti-inflammatory and pro-inflammatory cytokines before and after treatment. Applicants submit that studying the levels of anti- inflammatory cytokines and pro-inflammatory cytokines before and after treatment in an in vivo experiment are not equivalent to measuring cytokine levels in controls as the specification distinguishes between determining the levels before and after treatment and determining the levels in the treatment sample and the untreated control sample (page 17, 2nd and 3rd paragraphs).

(5) Neither Togawa et al. nor Hart et al., singularly or in combination, teach or suggest: (1) determining the ratio of at least one anti-inflammatory cytokine to at least one pro- inflammatory cytokine before and after treatment with a probiotic; (2) substituting a probiotic treatment for a lactoferrin treatment; or (3) determining the levels of various anti-inflammatory and pro-inflammatory cytokines before and after treatment with a probiotic. Applicants are left with the only conclusion that the Examiner has improperly used their application as a road map through impermissible hindsight reconstruction (page 18, 2nd paragraph, bridging page 19, 2nd paragraph).

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning (1 and 5), it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to (2): Applicants argue that determining the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment with a probiotic yields unexpected results with regard to determining the efficacy of a probiotic as a treatment for inflammatory diseases of the bowel. The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). A showing of unexpected results must be based on evidence, not argument or speculation. *In re Mayne*, 104 F.3d 1339, 1343-44, 41 USPQ2d 1451, 1455-56 (Fed. Cir. 1997). Togawa et al. teach "It has been reported that there is a disturbed balance between proinflammatory and anti-inflammatory cytokines in inflammatory bowel diseases" (page Gi87, 2nd column, 1st paragraph). The reference teaches that effective treatment, that is attenuation of colitis (in this instance, with

lactoferrin) is accompanied by and correlates with significant induction of the anti-inflammatory cytokines IL-4 and IL-10 and significant reductions in the proinflammatory cytokines TNF-α and IL-1β (abstract). Hart et al teach "Several strains of probiotics are able to alter the mucosal and systemic immune function". The probiotics have been shown to induce a systemic anti-inflammatory or Th2 response. A combination of probiotic bacteria has been shown to increase mucosal production of IL-10 (an anti-inflammatory cytokine) and reduce the secretion of TNF-α and IFN-γ (pro-inflammatory cytokines) (page 116, 2nd column, 3rd and 4th paragraph). In view of the teachings in the prior art, one of ordinary skill would conclude that a treatment that is effective in treating inflammatory bowel disease and ameliorating the symptoms of said disease, would also have the effect of increasing the levels of anti-inflammatory cytokines and decreasing the levels of pro-inflammatory cytokines. Such a shift would naturally result in an increase in the ratio of the levels of anti-inflammatory to pro-inflammatory cytokines. In light of the teachings in the prior art, such a shift, accompanying an effective treatment protocol, would not be unexpected.

In response to 3: Applicants assert that it would not have been obvious to one of ordinary skill in the art at the time the invention was made to substitute a method of determining the efficacy of a probiotic treatment of inflammatory diseases of the bowel in mammals as claimed for a method of determining the efficacy of lactoferrin treatment of inflammatory diseases of the bowel in mammals. Togawa et al. teaches that lactoferrin is a natural immunomodulator and is known to exert an anti-inflammatory effect (abstract). "Since lactoferrin showed anti-inflammatory and immunomodulatory effects, lactoferrin is expected to attenuate exaggerated activation of proinflammatory cytokines in TNBS colitis" (page G192, 2nd column, 2nd paragraph). Hart et al teach "probiotics may exert their effect through nonspecific modulation of the immune system" (page 116, 1st column, last paragraph bridging 2nd column, 1st paragraph); "selected strains of probiotics are able to alter the mucosal and systemic immune function. Lactobacillus strains have been shown to induce a systemic anti-inflammatory or Th2 response. The combination of probiotic bacteria in VSL#3 has been shown to increase mucosal production of IL-10 and reduce the secretion of tumor necrosis factor alpha

and interferon gamma" (page 116, 2nd column, 3rd paragraph). Thus, the art of record teaches that both lactoferrin and pro-biotics are effective in the treatment of IBD; both of these treatment modalities act by immunomodulation and have anti-inlammatory effects. It would thus be obvious to one of ordinary skill to substitute a method of determining the efficacy of a probiotic treatment for determining the efficacy of lactoferrin treatment since both treatments are taught as acting as immunomodulators and are anti-inflammatory agents, and would thus be equivalent therapeutic agents.

Contrary to the Attorney's argument, there are no teachings at paragraph 0008 that "the very nature of inflammatory diseases of the bowel means that screening and measuring the efficacy of potential treatments in human subjects is very difficult." The cited paragraph teaches "there is no cure and the exact causes of the disease are not yet understood" and goes on to list some conventional treatments. Among the treatments listed are anti-inflammatory drugs. Thus, the discussion in the background section of the specification teaches anti-inflammatory drugs are recognized in the art as effective treatments for IBD. Both lactoferrin and probiotics are taught in the art as exerting anti-inflammatory effects on IBD. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute a method of determining the efficacy of a probiotic treatment of inflammatory diseases of the bowel in mammals as claimed for a method of determining the efficacy of lactoferrin treatment of inflammatory diseases of the bowel in mammals.

In response to 4: Applicants argue that the cited reference do not teach or suggest determining the efficacy of probiotics in treatment of inflammatory bowel disease by determining the levels of various anti-inflammatory and pro-inflammatory cytokines before and after treatment and assert that specification teaches that "In the in vivo method, these levels are determined both before administration of the treatment, and determining the same ratio either during the treatment or following completion of the treatment. In the in vitro method, the levels of at least one anti-inflammatory cytokine to at least one pro-inflammatory cytokine are determined in the treatment sample, and an untreated control biological sample tested concurrently". The method

taught by Togowa et al teaches measuring the levels of anti-inflammatory and pro-inflammatory cytokines in TNBS-colitis rats receiving saline and TNBS-colitis rats receiving lactoferrin. One of ordinary skill in the art would recognize that TNBS-colitis rats receiving saline are the equivalent of untreated animals, or in terms of clinical research, the equivalent of patients before treatment. Thus it would be obvious of one of ordinary skill in the art, aware of the teachings of Togawa et al. which teaches the following facts:

(1) measurement of the various cytokines in IBD animals without treatment and IBD animals after lactoferrin treatment, and

(2) changes in cytokines profile (increase in anti-inflammatory cytokines, decrease in pro-inflammatory cytokines) correlates with attenuation of IBD symptoms and pathologies

would be motivated to determine the levels of anti-inflammatory and pro-inflammatory cytokines before and after treatment and would conclude that an increase in anti-inflammatory cytokines and a reduction in pro-inflammatory cytokines after treatment would be indicative of the efficacy of treatment as one would be aware that such modifications are routine in clinical research and in therapeutic protocols.

As discussed above, one of ordinary skill would be motivate to utilize such methods to determine the efficacy of another form of treatment, utilizing another anti-inflammatory therapy, pro-biotic administration, as the art teaches that lactoferrin and probiotic therapies are art-accepted equivalents (both are recognized as having immunomodulatory and anti-inflammatory effects).

To summarize Applicants arguments (page 18, last paragraph, bridging page 19, first paragraph, and response to said arguments:

(a) Applicants submit that due to the unexpected results yielded from the determination of the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment with a

probiotic, it would not have been obvious to one of ordinary skill in the art to determine the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment with a probiotic.

Response: An increase of the ratio of anti-inflammatory to pro-inflammatory cytokines following effective treatment of IBD is not an unexpected result, as discussed in detail above, as both Togawa et al. and Hart et al. teach that effective treatment with lactoferrin and probiotics, respectively, resulting in attenuation of colitis is accompanied by and correlates with significant induction of the anti-inflammatory cytokines and significant reductions in the proinflammatory cytokines. As discussed above, once levels of cytokines of interest are measured, it would be obvious to one of ordinary skill to express such levels as ratios of anti-inflammatory to pro-inflammatory cytokines to more easily and efficiently monitor the change in cytokine profiles.

(b) Applicants submit that because of the difficulties associated with determining the efficacy of potential treatments of inflammatory diseases of the bowel, it is in an unpredictable art, and it would not have been obvious to one of ordinary skill in the art to substitute a method of determining the efficacy of a probiotic treatment of inflammatory diseases of the bowel for a method of determining the efficacy of lactoferrin treatment of inflammatory diseases of the bowel from the teachings of Togawa et al. in view of Hart et al.

Response: Applicants point to teachings in the specification [Background, paragraph 008]. This paragraph teaches “Conventional treatments for IBD have involved anti-inflammatory drugs, immunosuppressive drugs and surgery”. The cited art, as discussed above, teaches that both lactoferrin and pro-biotics act as immunomodulatory and anti-inflammatory agents. These treatment modalities are considered to be art-accepted equivalents. It would thus be obvious to one of ordinary skill in the art to substitute a method of determining the efficacy of a probiotic treatment of inflammatory diseases of the bowel for a method of determining the efficacy of lactoferrin treatment of inflammatory diseases of the bowel, since both methods are thought to act on the same physiological system-both act as immunomodulators.

(c) Applicants submit that because studying the levels of anti-inflammatory cytokines and pro-inflammatory cytokines before and after treatment in an *in vivo* experiment are not equivalent to measuring cytokine levels in controls, it would not have been obvious to one of ordinary skill in the art to determine the levels of anti-inflammatory and pro-inflammatory cytokines before and after treatment in an in vivo experiment in the absence of controls.

Response: As discussed above, in addition to determining cytokine profiles in disease-free animals, Togawa et al. which teaches: (1) measurement of the various cytokines in IBD animals without treatment and IBD animals after lactoferrin treatment, and (2) changes in cytokines profile (increase in anti-inflammatory cytokines, decrease in pro-inflammatory cytokines) correlates with attenuation of IBD symptoms and pathologies. One of ordinary skill, aware of standard protocols in clinical research and in clinical practice, and aware of the teachings of Togawa et al, would recognize that TNBS-colitis rats receiving saline are the equivalent of untreated animals, or in terms of clinical research, the equivalent of patients before treatment, would be motivated to determine the levels of anti-inflammatory and pro-inflammatory cytokines before and after treatment and would conclude that an increase in anti-inflammatory cytokines after treatment would be indicative of the efficacy of treatment as one would be aware that such modifications are routine in clinical research and in therapeutic protocols.

The rejection is thus maintained.

The rejection of Claims 18 and 21 under 35 U.S.C. 103(a) as being unpatentable over Togawa et al. and Hart et al. as applied to claims 1, 17 and 20 in view of Vignali et al. (cited in previous Office Action) is maintained for reasons of record and for reasons set forth below. The teachings of Togawa et al. and Hart et al are outlined above. The references, singly or in combination, do not teach a method of measuring levels of at least one anti-inflammatory cytokine and at least one pro-inflammatory cytokine in a biological sample by multiplexed ELISAs using coded microspheres coupled with a flow cytometer detection system. Vignali et al teach a FlowMetrix System of quantifying the

concentration of 15 cytokines simultaneously in a 100 µl sample. The Luminex FlowMetrix system uses microspheres as the solid support for a conventional immunosorbent assay. Each bead set is comprised of microspheres manufactured with a uniform, distinct proportion of red and orange fluorescent dyes. Data are acquired on a conventional flow cytometer (page 246, 1st column, 1st paragraph).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Togawa et al and Hart et al which teach evaluating the efficacy of a probiotic treatment by measuring cytokine levels using an ELISA assay and substitute the multiplex assay taught by Vignali for the ELISA assay taught by Togawa et al. The person of ordinary skill in the art would have been motivated to make these modifications and anticipate success because Vignali teaches the multiplex system simultaneously measures many different analytes in a small sample volume (abstract), measuring a number of cytokines simultaneously in biological fluids and tissue culture samples.

Applicants traverse the rejection (Response of 21 June 2010, page 22, 5th paragraph). The reasons for the traversal are:

The Examiner rejected independent claim 1 on the basis of the teachings of Togawa et al. and Hart et al. as set forth above. The Examiner narrowly cited Vignali et al. for teaching a method of measuring levels of at least one anti-inflammatory cytokine and at least one pro- inflammatory cytokine in a biological sample by multiplexed ELISA's using coded microspheres coupled with a flow cytometer detection system; however, Vignali et al. fail to cure the deficiencies of Togawa et al. and Hart et al. as previously discussed.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

In response to applicants' traversal of rejection of Claim 1 over Togawa et al. and Hart et al, see above discussion.

As stated above, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Togawa et al and Hart

et al. and substitute the multiplex assay taught by Vignali for the ELISA assay taught by Togawa et al. One would be motivated to make this substitution, and anticipate success since both assays involve immunological methods of measuring cytokine concentrations and Vignali teaches a more efficient method of quantifying the concentration of 15 cytokines simultaneously. As stated above, knowing the results of measurements of cytokine levels, one would be motivated to compute ratios as a way of determining shifts in patterns of cytokine levels.

The rejection is therefore maintained.

The rejection of Claims 6-8 under 35 U.S.C. 103(a) as being unpatentable over Togawa et al. and Hart et al as applied to claim 1 and newly submitted claim 46 in view of Blumberg et al. (1999. Current Opinion in Immunology 11:648-656) is maintained and is now applied to newly submitted claims 47-49 for reasons of record and for reasons set forth below. The teachings of Togawa et al. and Hart et al are outlined above. Togawa et al do not teach method wherein the ratio of anti-inflammatory cytokine to pro-inflammatory cytokine is the ratio of the level of IL-10/to the level of IL-12 (claims 6 and 47), or the level of TGF-β/to the level of IL-12 (claims 7 and 48), or the level of IL-10/ to the level of IFN-γ (claims 8 and 49). Togawa et al. teaches measurement of anti-inflammatory cytokines IL-4 and IL-10 and measurement of pro-inflammatory cytokines TNF-α, IL-1β and IL-6 (abstract and Figure 5). Blumberg et al. teach immune responses uniquely involved in IBD pathogenesis and note the importance of balance of pro-inflammatory cytokines such as IFN-γ, TNF, and IL-12 and anti-inflammatory cytokines such as IL-10 and TGF-β (abstract). The reference teaches that IL-12 is a key factor in the pathogenesis of the TNBS-induced colitis model (the model taught by Togawa et al) and induces overproduction of IFN-γ and TNF (page 650, 2nd column, last paragraph bridging page 651, 1st column, 3rd paragraph). Blumberg et al also teach that mucosal inflammation can be viewed as a failure of production of suppressor cytokines such as TGF-β and IL-10 (page 652, 2nd column, 2nd paragraph).

Aware of the teachings of Blumberg, which identify pro- and anti-inflammatory cytokines crucial to the pathology of IBD, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Togawa et al and substitute measurement of the pro-inflammatory cytokines taught by Blumberg et al (IFN-γ and IL-12) for the pro-inflammatory cytokine taught by Togawa et al (TNF-α, IL-1β and IL-6) and the anti-inflammatory cytokine taught by Blumberg et al (TGF-β) for the anti-inflammatory cytokine taught by Togawa et al (IL-10). Once measurement of these cytokines is accomplished, the calculation of ratios would be obvious as a way of monitoring changes in the balance of levels of pro- to anti-inflammatory cytokines. One would be motivated to make these modifications because all three references teach the importance of disturbed balance between proinflammatory and anti-inflammatory cytokines in the pathology of inflammatory bowel disease and Blumberg et al teach IFN-γ, TNF, and IL-12 are pro-inflammatory cytokines involved in pathology of IBD (art-recognized equivalents) and IL-10 and TGF-β are anti-inflammatory cytokines (art-recognized equivalents) whose expression may be down-regulated in IBD. One would have expected success because methods of measuring cytokine levels in biological samples is well known in the art.

Applicants traverse the rejection (Response of 21 June 2010, page 20, 3rd paragraph bridging page 22, 1st paragraph). The reasons for the traversal are:

(1) Togawa et al., Hart et al., and Blumberg et al. are completely void of any teaching or suggestion of determining the efficacy of probiotics in the treatment of inflammatory diseases of the bowel by determining the ratio of the level of at least one anti-inflammatory cytokine to the level of at least one pro-inflammatory cytokine before and after treatment. Togawa et al., Hart et al., and Blumberg et al. are completely void of any teaching or suggestion of determining the efficacy of probiotics by determining the specific ratios of interleukin-10 to interleukin-12, transforming growth factor-β to interleukin-12, or interleukin 10 to interferon-γ.

(2) Determining the efficacy of a probiotic as a treatment of inflammatory diseases of the bowel in mammals in vivo is an unpredictable art. As discussed above, the specification of the present invention provides that, "[t]he control of inflammatory

diseases is exerted at a number of levels," (see Page 1, paragraph 0010), and that, "[t]he controlling factors include hormones, prostaglandins, reactive oxygen and nitrogen intermediates, leukotrienes and cytokines." (See Page 1, paragraph 0010). Additionally, the specification provides that, "[m]ultiple mechanisms exist by which cytokines generated at inflammatory sites influence the inflammatory response," (see Page 1, paragraph 0011), and further provides that "[m]ost cytokines are pleiotropic and express multiple biologically overlapping activities." (See Page 1, paragraph 0011). Moreover, the specification provides that, "as many cytokines may have both pro- and anti- inflammatory activities, it is very difficult to attribute disease symptoms, or recovery there from, with a particular individual cytokine." (See Page 1, paragraph 0011). The specification further provides that, "[w]ithout wishing to be bound by the theory, it is believed that the specific ratios described herein are pivotal to the progression or remission of inflammatory diseases of the bowel." (See Page 6, paragraph 0076). As a result, Applicants submit that it would not have been obvious to one of ordinary skill in the art to determine the efficacy of a probiotic as a treatment of inflammatory diseases of the bowel by determining the specific ratios of interleukin-10 to interleukin-12, of transforming growth factor-β to interleukin-12, and of interleukin 10 to the level of interferon-γ. Applicants submit that it would not have been obvious to one of ordinary skill in the art to modify the teachings of Togawa et al. by substituting measurement of the pro-inflammatory cytokines taught by Blumberg et al. (IFN- γ and IL-12) for the pro-inflammatory cytokine taught by Togawa et al. (TNF-α, IL-1β, and IL-6), and by substituting the anti-inflammatory cytokine taught by Blumberg et al. (TGF- β) for the anti-inflammatory cytokine taught by Togawa et al. (IL- 10), wherein cytokines exhibit multiple biologically overlapping activities, wherein determining the efficacy of potential treatments in humans for inflammatory diseases of the bowel is difficult, and wherein the art is unpredictable.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

In response to Applicants' traversal of the rejection of Claim 1 over Togawa et al. and Hart et al. See discussion above.

In response to Applicants' assertion that Togawa et al., Hart et al., and Blumberg et al. are completely void of any teaching or suggestion of determining the efficacy of probiotics by determining the specific ratios of interleukin-10 to interleukin-12, transforming growth factor-β to interleukin-12, or interleukin 10 to interferon-γ:

Towaga et al. teach measuring levels of the anti-inflammatory cytokines IL-4 and IL-10 and pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 and teaches a change in cytokine profile (activation of anti-inflammatory cytokines and suppression of pro-inflammatory cytokines) correlating with efficacy of treatment of IBD.

Hart et al teach probiotic therapy has an immunomodulatory effect, inducing a systemic anti-inflammatory or Th2 response, increasing mucosal production of IL-10 (an anti-inflammatory cytokine) and reducing the secretion of TNF-α and IFN- γ (pro-inflammatory cytokines).

Blumberg et al. teach immune responses ***uniquely*** involved in IBD pathogenesis and note the importance of balance of pro-inflammatory cytokines such as IFN-γ, TNF, and IL-12 and anti-inflammatory cytokines such as IL-10 and TGF-β (abstract). The reference teaches that IL-12 is a key factor in the pathogenesis of the TNBS-induced colitis model (the model taught by Togawa et al) and induces overproduction of IFN-γ and TNF (page 650, 2nd column, last paragraph bridging page 651, 1st column, 3rd paragraph). Blumberg et al also teach that mucosal inflammation can be viewed as a failure of production of suppressor cytokines such as TGF-β and IL-10 (page 652, 2nd column, 2nd paragraph).

Thus, the three cited references teach a shift in cytokine production, an increase in the anti-inflammatory cytokines **IL-4, IL-10, TGF-β** and a reduction in pro-inflammatory cytokines **TNF-α, IL-1β, IL-6, IFN- γ, and IL-12** correlates with the efficacy of treatment of IBD.

As noted by applicants, the background of the specification provides general teachings as to the causes and treatment of IBD and teaches that conventional treatments included administration of anti-inflammatory drugs (which would include lactoferrin and probiotics, as taught by Towaga et al. and Hart et al.). The specification provides general teachings about the role of cytokines in the inflammatory process. [paragraph 0011].

The references cited above (Togawa et al, Hart et al. and Blumberg) teach the importance of ***specific cytokines*** in the pathogenesis of IBD. The references teach the importance of the balance between specific anti-inflammatory cytokines **(IL-4, IL-10, TGF-β)** and pro-inflammatory cytokines (**TNF-α, IL-1β, IL-6, IFN- γ, and IL-12)** in the disease process. Both Togawa et al and Hart et al. teach a shift in cytokine profiles, an increase in anti-inflammatory cytokines and a decrease in pro-inflammatory cytokines correlate with the efficacy of treatment of IBD. One of ordinary skill, aware of the teachings of the cited art would conclude that anti-inflammatory cytokines **IL-4, IL-10, TGF-β** and pro-inflammatory cytokines **TNF-α, IL-1β, IL-6, IFN- γ, and IL-12** are art-accepted equivalents in the pathogenesis of IBD.

The measurement of levels of any one of the specifically listed anti- and pro-inflammatory cytokines before and after treatment would provide equivalent information about the efficacy of the administered treatment. While Towaga et al and Blumberg do not teach or suggest establishing or analyzing any ratios of cytokines to evaluate efficacy of treatments, once levels of cytokines are determined, the calculation of ratios would be obvious as a way of monitoring changes in the balance of levels of anti- to pro- inflammatory cytokines. Therefore, a method of measuring cytokine levels and calculating levels of anti- to pro-inflammatory cytokines wherein the ratio of anti-inflammatory cytokine to pro-inflammatory cytokine is the ratio of the level of IL-10/to the level of IL-12, or the level of TGF-β/to the level of IL-12, or the level of IL-10/ to the level of IFN-γ is obvious over the teachings of the prior art.

The rejection is therefore maintained.

The rejection of Claims 11 and 12 under 35 U.S.C. 103(a) as being unpatentable over Togawa et al. and Hart et al. as applied to claim 1 in view of Bing et al (1998. World J Gastroenterology 4:252-255, cited in previous Office Action) is maintained for reasons of record and for reasons set forth below.

The teachings of Togawa et al. and Hart et al. are outlined in detail above. The references, singularly or in combination, do not teach a method of determining the efficacy of a treatment of inflammatory disease of the bowel in mammals wherein said biological sample comprises peripheral blood mononuclear cells (PBMC) with *in vitro* stimulation (Claim 11), wherein said in vitro stimulation comprises stimulation with a mitogen (Claim 12).

Bing et al. teach assaying production of inflammatory cytokines such as TNF-α and IL-6 by PBMCs isolated from patients with IBS wherein said PBMCs are stimulated by a mitogen, PHA (phytohemagglutinin), thus teaching measurement of cytokine levels produced by PBMCs isolated from patients with IBS to be an equivalent method of determining cytokine profiles as measuring cytokine levels in biopsy samples from the bowel of IBS patients.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Togawa et al and Hart et al. and substitute measurement of the pro-inflammatory cytokines and anti-inflammatory cytokines in mitogen-stimulated PBMCs, the system taught by Bing et al, for measurement of cytokines in colonic tissue (biopsies) from control and treated animals (equivalent of “before" and “after” measurements of cytokine levels in human patients). One of ordinary skill in the art would have been motivated to make these modifications because the skilled artisan would recognize that it would be simpler and less invasive to obtain PBMCs from blood samples drawn from patients than to obtain biopsies from colon tissue. Once measurement of these cytokines is accomplished, the calculation of ratios would be obvious as a way of monitoring changes in the balance of levels of pro-

to anti- inflammatory cytokines. One would have expected success because methods of measuring cytokine levels in cell culture supernatants is well known in the art, and is taught by Bing et al.

Applicants traverse the rejection (Response of 21 June 2010, page 23, 2nd paragraph). The reasons for the traversal are:

The Examiner rejected independent claim 1 on the basis of the teachings of Togawa et al. and Hart et al. as set forth above. Bing et al. was narrowly cited for teaching measuring cytokine levels produced by peripheral blood mononuclear cells isolated from patients with IBS; however, Bing et al. fail to cure the deficiencies of Togawa et al. and Hart et al. as previously discussed.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

In response to the traversal of rejection of Claim 1 on the basis of the teachings of Togawa et al. and Hart et al., see the detailed discussion above.

The Bing reference is provided to establish that cytokines can be measured in supernatants of stimulated PBMCs as an alternative and less invasive method for evaluating changes in cytokine levels in mammalian subjects (stimulated PBMCs vs biopsies). Computing ratios of levels of anti-inflammatory cytokine to pro-inflammatory cytokine is a mental exercise or calculation step and would not confer patentability on the method of the instant invention. Once measurement of the recited cytokines is accomplished, the calculation of ratios would be obvious to the skilled artisan as a way of monitoring changes in the balance of levels of pro- to anti- inflammatory cytokines.

The rejection is thus maintained.

With respect to rejection of new claims 46-49: Applicants are directed to above discussions.

Conclusions:

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFER whose telephone number is (571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shulamith H. Shafer/
Examiner, Art Unit 1647